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Computational Analysis of Pharmacokinetic, Bioactivity and Toxicity Parameters of Some Selected Oral-hypoglycaemic Agents

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Abstract Diabetes mellitus is a chronic, lifelong condition that affects body's ability to use the energy found in food. The number of patients with DM is markedly increasing worldwide. Globally the prevalence of diabetes mellitus is increasing. The increase in prevalence has accelerated due to the aging population structure in the developed countries and due to the globally increasing obesity, as well as stressing life style. Diabetes mellitus is the sixth leading cause of death globally. There are several medications associated adverse effects occur. So, there is essential requirement for developing new antidiabetic agents to devoid such toxic effects. In this research investigation, we performed pharmacokinetic, toxicity and bioactivity study of some antidiabetic agents by applying computational methods.

Keywords GPCR Ligand, PSA, LogP, QSAR, Oncogenicity

Introduction

Diabetes mellitus is a complex set of metabolic disorders characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [1]. Recent evidence suggests that oxidative stress may contribute to the pathogenesis of Type-2 Diabetes Mellitus by increasing insulin resistance or impairing insulin secretion. Globally, the number of people suffering from diabetes is increasing at an alarming rate [2].

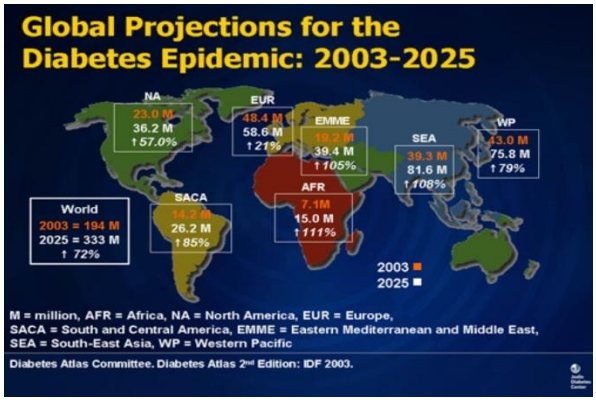

Figure 1: Worldwide prevalence of diabetes mellitus 2003-2025

American diabetes association criteria include symptoms like polyuria, polydipsia and unexplained weight loss, ketosuria, weakness. A fasting blood glucose level of 126 mg/dl and 200 mg/dl post prandial (oral Glucose load) is considered as indication of DM. Globally the prevalence of diabetes mellitus is increasing. The increase in prevalence has accelerated due to the aging population structure in the developed countries and due to the globally increasing obesity, as well as stressing life style. Diabetes mellitus is the sixth leading cause of death globally [3].

In recent years, developed nations have witnessed an explosive increase in the prevalence of DM predominantly related to lifestyle changes and the resulting surge in obesity. The metabolic consequences of prolonged hyperglycemia and dyslipidemia, including accelerated atherosclerosis, chronic kidney disease and blindness, pose an enormous burden on patients with diabetes mellitus and on the public health system [4]. The number of patients with DM is markedly increasing worldwide. DM is associated with impaired glucose metabolism that leads to an increase in free radical production and increase in triglyceride and lipoprotein levels.

Antidiabetic agents aim to reduce blood sugar levels to an acceptable range and relieve symptoms of diabetes such as thirst, excessive urination and ketoacidosis. Antidiabetic agents also prevent the development of, or slow the progression of, long-term complications of the disease, such as nephropathy, neuropathy, and retinopathy. Antidiabetic agents refer to all the different types of medicine involved in the treatment of diabetes.

Sulfonylurea, Insulin, Thiazolidinediones, Non-sulfonylureas, Incretin mimetics, Dipeptidyl peptidase 4 inhibitors, Amylin analogs, Alpha-glucosidase inhibitors, Biguanides and SGLT-2 inhibitors are the various medications for treatment of diabetes mellitus. There are several medications associated adverse effects occur.

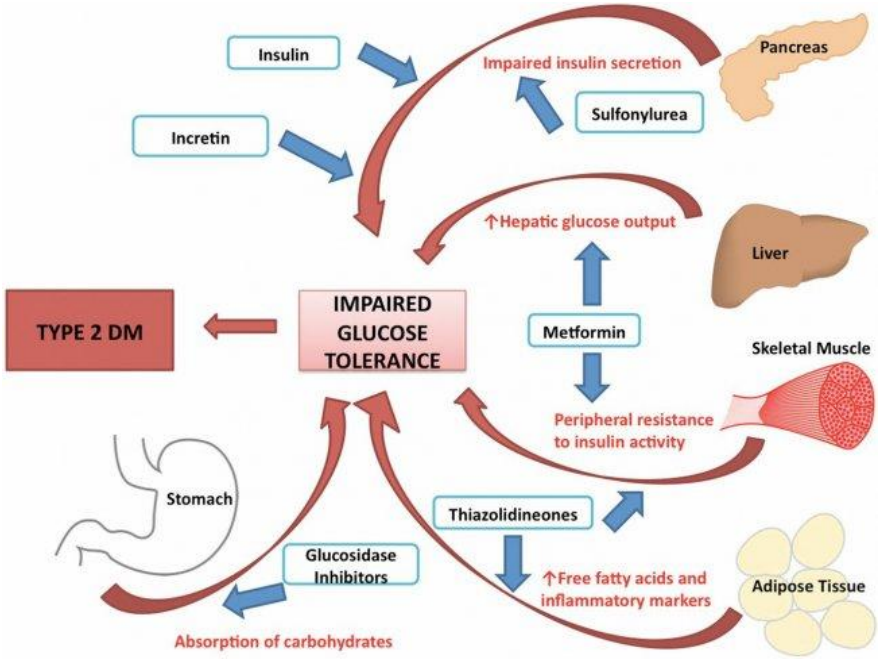

Figure 2: Treatment approach for diabetes mellitus

So, there is essential requirement for developing new antidiabetic agents to devoid such toxic effects. The aim of this research work is to study pharmacokinetic, toxicity and bioactivity profile of some antidiabetic agents by applying computational methods.

Materials and Methods

Pharmacokinetic study

There are various physicochemical descriptors and pharmacokinetic relevant properties of the oral hypoglycaemic agents were evaluated by using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com).

Molinspiration Cheminformatics offers broad range of tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches.

This software also supports fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java; therefore can be used practically on any computer platform [5]. Drug-likeness is described as a complex balance of various molecular properties and structural features which determine whether particular molecule is similar to the known drugs. Drug-likeness evaluated by the Lipinski rule of five that deals four simple physicochemical parameter ranges (MWT ≤ 500, log P ≤ 5, Hbond donors ≤ 5, H-bond acceptors ≤ 10) associated with 90% of orally active drugs that have passed phase II clinical status [6]. Other calculation methods such as ligand efficiency and lipophilic efficiency can also be used to express drug-likeness as parameters of potency.

In silico Bioactivity analysis

The bioactivity score of selected agents were also evaluated using the tool Molinspiration Cheminformatics server (http://www.molinspiration.com). In this computational chemistry technique large chemical databases are analyzed in order to identify possible new drug candidates. In the Molinspiration tool, the miscreen engine first analyze a training set of active structures (in extreme case even single active molecule is sufficient to built a usable model) and compares it with inactive molecules by using sophisticated Bayesian statistics [7]. Only SMILES or SDfile structures of active molecules are sufficient for the training, no information about the active site or binding mode is necessary. This is particularly useful in projects where structure-based approach cannot be applied because information about 3D receptor structure is not available, for example in screens aiming to find ligands modulating Gprotein coupled receptors [8]. Based on this analysis a fragment-based model is developed, where for each substructure fragment a bioactivity contribution is calculated. Once a model is build the bioactivity of screened molecules may be then calculated as a sum of activity contributions of fragments in these molecules. This provides a molecule activity score (a number, typically between -3 and 3).

Molecules with the highest activity score have the highest probability to be active. Such *in silico* screening is very fast, large collections of molecules (more than 100'000 molecules) may be screened in an hour [9].

In silico Toxicity study

The toxicity of the selected oral hypoglycaemic agents was evaluated by computational method using Pallas version 3.1 ADMETox prediction software pentium IV processor. This software tool was started by double click on the icon. The molecule to be predicted was drawn by double click on new option, and then molecule was subjected for evaluation of toxicity by selecting ToxAlert options [10, 11 and 12].

Result and Discussion

There were eight oral hypoglycaemic agents selected and analyzed to pharmacokinetic parameters and drug likeness (Lipinski's rule of five) which are given in Table 1.

Table 1: ADME Properties of oral hypoglycaemic agents

Name	Molecular formula	Molecular weight	Log P	TPSA	nON	nOHNH	nrotb	volume	*In silico* absorption %
Tolbutamide	$C_{12}H_{18}N_2O_3S$	270.35	2.54	75.27	5	2	5	242.79	83.03
Chlorpropamide	$C_{10}H_{13}ClN_2O_3S$	276.75	2.21	75.27	5	2	4	222.96	83.03
Tolazamide	$C_{14}H_{21}N_3O_3S$	311.41	1.35	78.50	6	2	3	278.58	81.91
Gliclazide	$C_{15}H_{21}N_3O_3S$	323.42	1.45	78.50	6	2	3	284.59	81.91
Metformin	$C_4H_{11}N_5$	129.17	-1.13	88.99	5	5	3	126.83	78.29
Miglitol	$C_8H_{17}NO_5$	207.23	-2.79	104.3	6	5	3	189.18	72.98
Rosiglitazone	$C_{18}H_{19}N_3O_3S$	357.44	2.35	71.53	6	1	7	314.51	84.32
Nateglinide	$C_{19}H_{27}NO_3$	317.43	2.56	66.40	4	2	6	316.03	86.09

All selected agents have molecular weight in the acceptable range (MWT ≤ 500). Low molecular weight containing molecules are easily absorbed, diffused and transported as compared to high molecular weight compounds.

As molecular weight increases except certain limit, the bulkiness of the molecules are also increases comparably. [13, 14] The MLogP (octanol / water partition coefficient) of all agents were calculated and found to be within acceptable range according to Lipinski's rule. The MLogP value is used to calculate the lipophilic efficiency that measures the potency of drug. Therefore Octanol-water partition coefficient logP value is essential in rational drug design and QSAR studies. In the pharmacokinetic study, hydrophobicity of the molecule is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption. TPSA (Topological Polar Surface Area) is a very useful physiochemical parameter of molecule that gives the information about polarity of compounds. This parameter was evaluated for analyzing drug transport properties.

Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen. Percent absorption were also evaluated for all selected oral hypoglycaemic agents by %ABS = 109- (0.345 * TPSA) [15].

Molecular volume assesses the transport properties of the molecule such as blood-brain barrier penetration. The number of rotatable bond was calculated and have found relevant. A molecule which have more number of rotatable bond become more flexible and have good binding affinity with binding pocket.

Bioactivity of all selected oral hypoglycaemic agents was evaluated against six different protein structures. Biological activity is measured by bioactivity score that are categorized under three different ranges-

1. If bioactivity score is more than 0.00, having considerable biological activity.
2. If bioactivity score is 0.5 to 0.00, having moderately activity.
3. If bioactivity score is less than -0.50, having inactivity. [16]

The result of this study was found that the selected agents are biologically active and have physiological effect. The bioactivity score profile of the all selected agents is given in Table 2.

Table 2: Bioactivity of oral hypoglycaemic agents

Name	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor Ligand	Protease inhibitor	Enzyme inhibitor
Tolbutamide	0.04	-0.12	-0.60	-0.63	0.13	0.13
Chlorpropamide	0.02	-0.06	-0.66	-0.75	0.07	0.11
Tolazamide	0.06	-0.37	-0.24	-0.41	0.16	0.07
Gliclazide	0.19	-0.35	-0.34	-0.37	0.17	0.01
Metformin	-1.44	-0.81	-2.47	-3.48	-1.11	-1.59
Miglitol	-0.40	-0.10	-0.53	-0.82	0.11	0.36
Rosiglitazone	0.16	-0.64	-0.61	0.35	-0.21	-0.07
Nateglinide	0.34	0.12	-0.30	0.08	0.59	0.16

The bioactivity score provide the information about the binding cascade of the drugs that is used for the development of a new functional drug with increased binding selectivity profile and less undesirable effects.

All selected oral hypoglycaemic agents were evaluated to toxicity profile and given in Table 3.

Table 3: Toxicity Profile of oral hypoglycaemic agents

Name	Toxicity	Overall toxicity	Oncogenicity	Mutagenicity	Teratogenicity	Irritation	Sensitivity	Immunotoxicity	Neurotoxicity
Tolbutamide	Highly Probable	76	76	71	17	0	0	0	0
Chlorpropamide	Highly Probable	76	76	0	18	0	0	0	0
Tolazamide	Highly Probable	76	76	71	29	47	0	0	0
Gliclazide	Highly Probable	76	76	67	29	47	0	0	0
Metformin	Not Probable	0	0	0	0	0	0	0	0
Miglitol	Not Probable	19	0	0	19	0	0	0	0
Rosiglitazone	Highly Probable	76	76	0	0	0	0	0	0
Nateglinide	Highly Probable	76	76	0	19	0	0	0	0

All of the drugs were found to be highly probable to toxicity except metformin and miglitol.

These research findings provide the lead for the design and development of new potent antidiabetic drugs. Computational study of all selected oral hypoglycaemic drugs gives the information about the pharmacokinetics of the existing drugs that provide the lead for development of functional drug with more effectiveness and lesser toxicity.

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